

PB88-162409

Health and Environmental Effects
Profile for Cyanazine

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84



U.S. Department of Commerce
National Technical Information Service

NTIS

2888-162409

EPA/600/X-84/243
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR CYANAZINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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CINCINNATI, OH 45268

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U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA (Please read instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-84/243	2.	3. RECIPIENT'S ACCESSION NO. P588 162409/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Cyanazine		5. REPORT DATE January 1984
7. AUTHOR(S)		6. PERFORMING ORGANIZATION CODE
8. PERFORMING ORGANIZATION NAME AND ADDRESS Same as box 12.		9. PERFORMING ORGANIZATION REPORT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		
16. ABSTRACT The Health and Environmental Effects Profile for <u>cyanazine</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Cyanazine</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>cyanazine</u> is 6×10^{-3} (mg/kg bw/day) for oral exposure.		
17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 44
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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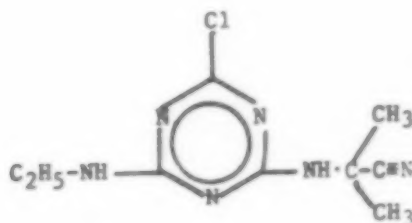
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
UV	Ultraviolet
w/v	Weight per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Cyanazine is the common name for 2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-1,3,5-triazine. Current Chemical Abstract usage is 2-[[4-chloro-6-(ethylamino)-1,3,5-triazin-2-yl]amino]-2-methylpropanenitrile and was formerly 2-[[4-chloro-6-(ethylamino)-s-triazin-2-yl]amino]-2-methylpropionitrile. It was first marketed in 1971 under the trademarks "Bladex" and "Fortrol" (BCPC, 1977). Other tradenames include Fortol, SD 15418, Payze, VL19804 and DW 3418. The structure and molecular formula for cyanazine are as follows:



Molecular weight: 240.7

Molecular formula: $C_9H_{13}ClN_6$

The Chemical Abstract Service (CAS) Registry number is 21725-46-2.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Cyanazine is a white crystalline solid. Selected physical properties are listed below (BCPC, 1977; WSSA, 1979):

Melting point:	166.5-167.0°C
Bulk density:	0.35 g/cc (fluffed) 0.45 g/cc (packed)

Vapor pressure:

<u>Temperature (°C)</u>	<u>mm Hg</u>
20	1.6×10^{-8}
30	1.0×10^{-8}
40	5.9×10^{-9}
20	7.5×10^{-9} (Grayson and Fosbraey, 1982)
70	1.9×10^{-8} (Grayson and Fosbraey, 1982)

Solubilities:

<u>Solvent</u>	<u>Temperature (°C)</u>	<u>Solubility</u>
acetone	25	19.5% w/v
benzene	25	15 g/l
carbon tetrachloride	20	1.0% w/v
chloroform	25	210 g/l
ethanol	25	45 g/l
hexane	25	15 g/l
water	23	160 ppm
water	25	171 ppm

Soil sorption coefficient (K_{oc})
(Kenaga, 1980):

experimental	200
calculated from water solubility	260

BCF (Kenaga, 1980):

calculated from K_{oc}	10
calculated from water solubility	34

Log octanol/water partition
coefficient:

2.24 (Brown and Flagg, 1981)

Cyanazine is stable to heat and light and to hydrolysis in neutral and slightly acidic or basic media (BCPC, 1977). It is stable to UV irradiation under practical conditions (WSSA, 1979).

1.3. PRODUCTION DATA

Cyanazine is prepared by reacting cyanuric chloride with ethylamine and 2-amino-2-methylpropionitrile (SRI, 1976).

SRI (1983) lists Shell Chemical in Mobile, Alabama, as a manufacturer, while USITC (1983) lists Ciba-Geigy as a manufacturer. It has been reported that Ciba-Geigy and Vicksburg Chemical have made cyanazine for Shell in the past (SRI, 1976). Current production figures are not available. The capacity of Shell's triazine facility is reportedly 50 million pounds/year (SRI, 1976).

1.4. USE DATA

Cyanazine is used as a pre- and post-emergent herbicide for the control of annual grasses and broadleaf weeds in corn, grain sorghum, cotton, peanuts, wheat fallow, barley and soybeans. Rates of application vary from 0.8-4 lb/acre or 0.25-3 kg/ha, depending upon crop and time of application (BCPC, 1977; WSSA, 1979).

In 1975, domestic consumption of cyanazine was estimated to be 7.3 millions pounds, with 7.2 million pounds used in corn and 0.1 million pounds in grain sorghum (SRI, 1976). Domestic consumption in 1976 was as follows: corn, 10.4; sorghum, 0.16; and soybeans, 0.015 million pounds, respectively (Eichers et al., 1978). By 1982, domestic consumption of cyanazine in corn had risen to 20.7 million pounds; in addition, 0.6 million pounds were used in cotton fields (USDA, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

Like other chemicals, the fate of cyanazine in water will depend on its ability to undergo chemical, photochemical and biological reactions and partitioning (transport) from the water column into air or sediment. No data were identified on the transport of cyanazine in water, but evaporation seems to be an unlikely process because of the low vapor pressure and relatively high water solubility. Also, adsorption to sediments seems unlikely because of the low K_{oc} value. The hydrolysis of cyanazine in water has been studied by Brown et al. (1972) using a ^{14}C -ring labeled compound over a temperature range of 25-75°C and pH 1.5-12. Brown et al. (1972) determined that the total hydrolysis rate constant, and hence the half-life, of the hydrolysis reaction of cyanazine at any temperature and pH value could be calculated using the specific acid/base catalytic relation:

$$k_{rate} = k_H[H^+] + K_{OH}^- [OH^-]$$

The rate constants and half-lives of cyanazine hydrolysis at various temperatures and pH are listed in Table 2-1. It is evident from these data that the hydrolysis rate is highly dependent upon the temperature and pH of the environment. From graphical representations in Brown et al. (1972), the hydrolysis half-life of cyanazine under environmentally significant conditions (25°C and pH 5.5-8.5) is, at a minimum, ~5000 hours (208 days). Therefore, hydrolysis alone will not be environmentally important as a removal mechanism unless it is catalyzed by some agent present in the aquatic environment such as soil colloids, humic acids or microbes.

Brown et al. (1972) also determined the products of cyanazine hydrolysis. The end-product of both acid and alkaline condition hydrolysis was

TABLE 2-1

Rate Constants and Half-Lives of Hydrolyses of Cyanazine*

pH	Temperature (T°C)	Rate Constant [(k _{rate})hr ⁻¹]	Half-Life $\frac{1}{k}$ h
1.55	25	2.31×10^{-2}	30
1.60	40	6.67×10^{-2}	10.4
1.55	55	2.31×10^{-1}	3.0
1.55	75	8.16×10^{-1}	0.85
4.00	25	3.38×10^{-2}	205
3.95	40	1.10×10^{-2}	63
3.90	55	3.46×10^{-2}	20
3.80	75	9.24×10^{-2}	7.5
5.70	55	1.48×10^{-4}	4676
5.50	75	6.39×10^{-4}	1085
7.70	55	1.13×10^{-4}	6110
7.40	75	1.16×10^{-3}	600
9.90	25	9.69×10^{-5}	7153
9.70	40	6.26×10^{-4}	1109
9.55	55	5.92×10^{-3}	117
9.20	75	4.95×10^{-2}	14
12.20	25	7.22×10^{-3}	96
11.25	55	8.25×10^{-2}	8.4
10.80	75	7.70×10^{-1}	0.90

*Source: Brown et al., 1972

2-hydroxy-4-carboxyisopropylamino-6-ethylamino-1,3,5-triazine. The intermediate 2-chloro-4-amidoisopropylamino-6-ethylamino-1,1,5-triazine was isolated during alkaline conditions. In a later study, Grayson (1980) found a similar hydrolysis mechanism of cyanazine in sulfuric acid solution. The hydrolysis involves primary attack at the nitrile group to give first the corresponding amide and then the carboxylic acid, followed by subsequent displacement of the chlorine atom with the hydroxyl group.

Data specific to the photodegradation, microbial degradation or volatilization of cyanazine in aquatic media were not found in the available literature. The transport of cyanazine via runoff water and sediments is discussed in Sections 2.3. and 3.1.

Kenaga (1980) has predicted BCFs for cyanazine, based upon water solubility and soil adsorption coefficient (K_{oc}), to be 34 and 10, respectively. A BCF of ≥ 1000 has a high potential for bioconcentration, while BCF values < 100 are unlikely to bioconcentrate. Yu et al. (1975) found no evidence to indicate that cyanazine or its degradation products are concentrated through the food chain in a model aquatic ecosystem.

The persistence and fate of cyanazine has been studied in a model aquatic ecosystem (Yu et al., 1975). After 35 days in the ecosystem, only 18% of the initial cyanazine remained undegraded in the water. The water also contained the cyanazine metabolites as follows: 60% N-deethylcyanazine; 0.8% cyanazine amide; 0.3% N-deethylcyanazine amide; 1.2% unknown polar metabolites; and 19% unextractable metabolites.

2.2. AIR

Specific data regarding the fate or transport of cyanazine in the atmosphere were not located in the available literature. Cupitt (1980) suggested that adsorption to particulate matter will be a reasonable vapor-phase

removal mechanism only for chemicals with a saturation vapor pressure of $\leq 10^{-7}$ mm Hg. Since the vapor pressure of cyanazine at 20°C is on the order of 10^{-6} to 10^{-5} mm Hg (Section 1.2.), it may be expected to remain strongly sorbed to particulate matter in the air.

2.3. SOIL

The fate and transport of cyanazine in soil has been studied more thoroughly than its fate and transport in the atmosphere or in aquatic media. However, more information is required to conclusively identify the predominant removal mechanisms by which cyanazine is lost from soil. While WSSA (1979) has reported that cyanazine is primarily degraded in the soil by microbes, published data are not available to confirm or to contradict this statement. It has been suggested that hydrolysis may be the primary mechanism for the decomposition of cyanazine in soil (Sironi et al., 1973; Majka and Lavy, 1977). The soil decomposition pathway and products of cyanazine have been identified (Beynon, 1972a,b; Sironi et al., 1973; Muir and Baker, 1978). These studies indicate that the cyanazine molecule is initially changed by hydrolysis of the nitrile group successively to the amide, then to the carboxylic acid, and then hydrolysis of the 2-chloro group to the hydroxy derivative. The amide, carboxylic acid and hydroxy derivative have all been identified in soil decomposition studies with cyanazine. This hydrolysis mechanism is identical to the aqueous hydrolysis of cyanazine discussed in Section 2.1. However, the hydrolysis rates of cyanazine, under environmental conditions as discussed in Section 2.1., are much too slow to account for the rapid degradation of cyanazine in soil (average half-life of 2 weeks; WSSA, 1979). Therefore, for chemical hydrolysis to be a significant removal mechanism, it must be undergoing catalysis by some agents present in the soil, such as soil colloids, humic acids, minerals or organic content. It is possible that microorganisms are catalyzing the hydrolysis.

White (1976) has reported that the s-triazine herbicides can react with mineral surfaces first by adsorption, followed by degradation through protonation and hydrolysis. White (1976) found that cyanazine absorbed to calcium montmorillonite may undergo some hydrolysis; however, the environmental significance of this reaction is not clear.

Data specific to the microbial degradation of cyanazine were not found in the available literature. Sirons et al. (1973) has suggested that microbial attack of the cyanazine molecule occurs after hydrolysis of the nitrile group.

The loss of cyanazine from soil due to photodecomposition under field conditions is reported to be minimal (WSSA, 1979). Additional data concerning cyanazine photolysis were not located in the available literature.

Plant uptake can remove small amounts of cyanazine from treated soils, as cyanazine is readily absorbed by foliage (WSSA, 1979). Beynon et al. (1972b) have studied the breakdown of cyanazine in maize and maize sap. In the sap, ~80% of absorbed cyanazine was degraded within 24 hours.

The transport of cyanazine from soil by physical processes such as leaching and runoff has been studied by various investigators. The leachability of cyanazine from soil is expected to be related to its adsorption capacity. The mobility of cyanazine in soil was measured by Majka and Lavy (1977) by means of soil thin-layer chromatography plates. They determined that cyanazine has an intermediate mobility in silty clay loam (R_f of 0.39), and a mobile mobility in sandy loam (R_f of 0.74). In addition, Majka and Lavy (1977) found that in the field, surface-applied cyanazine did not move below 5 cm in silty clay loam while in soil columns in the laboratory, surface-applied cyanazine penetrated 20 cm when leached over comparable time with similar amounts of water. Muir and Baker (1978) detected

cyanazine in the 20-40 cm depth layer 12 months after application in the field on sandy loam soil. Kenaga (1980) experimentally determined a soil adsorption coefficient (K_{oc}) for cyanazine to be 200. Compounds having a K_{oc} value near 1000 are considered immobile, while K_{oc} values <100 are considered to be moderately to highly mobile. Brown and Flagg (1981) have measured a K_{oc} value of 182 for cyanazine in silty soil. Weber (1970) has shown that cyanazine adsorption is related to pH for Na-montmorillonite; adsorption increases with a decrease in pH. Anderson et al. (1980) have shown that as much as 80% of the cyanazine adsorbed by various Canadian soils can be desorbed under laboratory conditions. WSSA (1979) has reported that cyanazine is reversibly adsorbed to soil particles, and that the degree of adsorption varies with soil texture, content of water and content of organic matter.

The loss of cyanazine from soil due to transport in runoff water has been shown to be relatively small. In a study of two watersheds in Georgia, Leonard et al. (1979) found that only $\leq 1\%$ of applied cyanazine was lost in runoff from rainfall. Yoo et al. (1981) and Muir and Baker (1976, 1978) monitored the runoff from cornfields that were drained by separate tile drains and found that losses of applied cyanazine represented only 0.01-0.02% of the total cyanazine applied. Baker and Johnson (1978) noted that runoff losses are affected by tillage practices and that losses are reduced by conservation tillage. Also, runoff losses can be significantly higher when rainfall occurs immediately after field application.

The loss of cyanazine from soil due to volatilization under field conditions is reported to be minimal (WSSA, 1979). Additional data concerning cyanazine volatilization were not located in the available literature.

Finally, the persistence of cyanazine in soil as a result of all the chemical, microbial and physical processes has been studied by a number of authors. Beynon et al. (1972a) analyzed soils from field trials in 1967-1970 and found the half-life of cyanazine to range from 1.3-5 weeks, with the degradation rate independent of thin-crop cover and possibly more rapid in moist soils. In the laboratory, Beynon et al. (1972b) tested the persistence of cyanazine in maize soils against atrazine and simazine and found that cyanazine degraded more rapidly than the other two herbicides; the cyanazine was degraded >90% within 32 days. Muir and Baker (1978) monitored the degradation of cyanazine over a 3-year period in soils under maize production. The soils were mainly loamy sands and sandy clay loams. The calculated half-lives of cyanazine observed during this 3-year study ranged from 10.8-24.1 days. Majka and Lavy (1977) examined cyanazine degradation over a 20-week period and varying temperatures (5, 20, 35 and 50°C) in a silty clay loam and in a fine sandy loam. In general, the cyanazine was decomposed within 10 weeks at 5°C and within 5 weeks at the higher temperatures; the initial observed half-life was ~1.5-2 weeks at the higher temperatures. Beynon et al. (1972a) suggested that cyanazine degradation at -10°C is not very likely. Sirons et al. (1973) conducted field experiments in Ontario, Canada, and found that cyanazine applied as a pre-emergent to clay loam soil degraded 50% in ~1 month, while it degraded 50% in ~1 week when applied as a post-emergent. Libik and Romanowski (1976) tested the persistence of cyanazine at two application rates (2.24 and 4.48 kg/ha) in the field (Lafayette, Indiana) in sandy and silt loam soils during 1972 and 1973; the cyanazine was degraded within 20-140 days. Anderson et al. (1980) have noted that >50% of the cyanazine applied to a Canadian clay loam soil degraded over a 3-week period. Yoo et al. (1981) applied cyanazine to two

cornfields in Quebec, Canada, and measured a half-life of 6 days. WSSA (1979) reported that the resultant average persistence of cyanazine at recommended rates is a half-life of ~2 weeks under conditions favorable for plant growth.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET data base (see Appendix) reports the analysis of cyanazine in 1790 samples of water and whole water (water plus sediment). The concentrations of cyanazine ranged from 0.0-900 $\mu\text{g}/\text{L}$, with the mean concentration $<3 \mu\text{g}/\text{L}$. A total of seven sediment only samples were analyzed and found to have a mean concentration of 0.037 mg/kg, with a range of 0.008-0.10 mg/kg.

Cyanazine has been identified in the drinking water in New Orleans, Louisiana, in concentrations ranging from <0.01 -0.35 $\mu\text{g}/\text{L}$ (Keith et al., 1976).

The concentrations of cyanazine in runoff from field application of the herbicide have been monitored by several investigators. Leonard et al. (1979) measured the cyanazine levels in both water and sediment from runoff in two watersheds in Georgia during a 90-day period following application; water levels ranged from 0-180 $\mu\text{g}/\text{L}$, sediment levels ranged from 0-2.3 mg/kg, and 87-88% of the detected cyanazine was in solution phase. Two days after the application of cyanazine at a rate of 2.24 kg/ha, the concentration of cyanazine in runoff (water plus sediment) from three locations in Iowa was observed to be 101-275 ppb (Baker et al., 1976). Yoo et al. (1981) applied cyanazine to a cornfield in Canada with a tile drain. Concentration of cyanazine in the tile-drain water was 111 ng/L 6 days after application, and then fell to levels of 3-17 ng/L in the following 6 months.

Leung et al. (1982) monitored the levels of cyanazine upstream, downstream and at a newly built reservoir on the Des Moines River in Iowa during September 1977 through November 1978. The authors noted that ~79% of the watershed upstream from Des Moines was corn and soybean cropland from which

agricultural runoff was a major source of pollution in the river. Cyanazine concentrations were found to be relatively the same upstream, downstream and at the reservoir during each month. Only dissolved cyanazine was detected. Highest concentrations, 71-457 ng/l, were monitored during the agriculturally active months of May through August. Levels detected during September through December were 2-151 ng/l, while levels of zero were found January through April.

The water from 237 wells from Ontario, Canada, were analyzed over the 10-year period 1969-1978 for herbicide contamination (Frank et al., 1979). Cyanazine was detected in two wells at a level of 0.1-1.0 µg/l in one well, and 1.0-10.0 µg/l in the other well. Roberts et al. (1979) detected cyanazine in 0.6% of water samples taken from the Hillman Creek watershed in Ontario, Canada, during 1973 and 1974. Kovacs-Huber (1982) found cyanazine levels of <4 ppb in Lake Balaton, Hungary.

3.2. FOOD

Pertinent data regarding exposure to cyanazine in food were not located in the available literature. WSSA (1979) has noted that cyanazine is readily absorbed by foliage through the roots and translocated to the leaves; however, it does undergo degradation.

3.3. INHALATION

Pertinent data regarding inhalation exposure to cyanazine were not located in the available literature.

3.4. DERMAL

Pertinent data regarding dermal exposure to cyanazine were not located in the available literature. (See Appendix for literature searched; also additional confidential information is available. See Chapter 8 for a more complete explanation.)

4. PHARMOCOKINETICS

4.1. ABSORPTION

Although the toxicity of cyanazine has been demonstrated upon dermal and oral administration (NIOSH, 1977), specific data regarding the uptake of the compound were not located in the available literature.

Absorption of orally-administered cyanazine undoubtedly occurs, as ~33% of a gavage dose of (2,4,6- ^{14}C)-labeled cyanazine in arachis oil appeared in the urine of rats within 24 hours of administration (Hutson et al., 1970). In a bile duct cannulated rat to which 1 mg of (2,4,6- ^{14}C)-labeled cyanazine in peanut oil was administered, a total of 21% of the radioactivity was detected in the bile within 20 hours of administration (Crayford and Hutson, 1972.)

4.2. DISTRIBUTION

Orally-administered cyanazine is rapidly metabolized in the liver and excreted via the urine and feces (Crayford and Hutson, 1972). Evidence for the enterohepatic cycling of cyanazine in rats was presented by Hutson et al. (1970). Up to 10% of the radioactivity-containing single oral dose was found in the fecal metabolites of rats 4 days after administration. This suggests that a portion of the dose was subject to enterohepatic cycling. About 3% of the orally-administered dose of (2,4,6- ^{14}C)-labeled cyanazine remained in the carcasses of rats 4 days after administration (Hutson et al., 1970).

4.3. METABOLISM

Hutson et al. (1970) used (2,4,6- ^{14}C)- and ^{14}C -ethyl-labeled cyanazine to elucidate the metabolism of the compound in Carworth Farm E rats. Three male and three female rats were given a single gavage dose of 0.8 mg (14 $\mu\text{Ci}/\text{mg}$) of the (2,4,6- ^{14}C)-labeled compound in arachis oil. One

male and one female were housed in closed, ventilated metabolism cages, and their expired $^{14}\text{CO}_2$ was collected. The remaining rats were kept in metabolism cages. One male rat was given a gavage dose of 1.22 mg (8.55 $\mu\text{Ci}/\text{mg}$) of the ^{14}C -ethyl-labeled compound in arachis oil. The urine and feces of all animals were collected for 4 days, after which they were killed and their carcass, skin and gut were assayed for radioactivity.

After 4 days, the urine, feces, carcass, skin and gut of animals given the (2,4,6- ^{14}C)-labeled compound contained ~41, 47, 2, 0.6 and 2.7% of the radioactivity administered, respectively. The expired air collected for 4 days contained 0 and 47.7% of the radioactivity contained in the (2,4,6- ^{14}C)- and ^{14}C -ethyl-labeled compound, respectively. The urine, feces and carcass of the rat given the ^{14}C -ethyl compound contained ~17, 26 and 5% of the administered radioactivity, respectively. Eight urinary metabolites were detected in rats given the (2,4,6- ^{14}C)-labeled compound. About 40 and 15% of the excreted metabolic products corresponded to N-acetyl-S-[4-amino-6-(1-methyl-1-cyanoethylamino)-s-triazinyl-2]-L-cysteine and 2-chloro-4-amino-6-(1-methyl-1-cyanoethylamino)-s-triazine, respectively. The authors stated that N-desethylation and formation of mercapturic acids were the major metabolic routes of cyanazine in the rat.

Crayford and Hutson (1972) further investigated the metabolism of (2,4,6- ^{14}C)- and ^{14}C -ethyl-labeled cyanazine in the rat. Groups of one male and one female Carworth Farms E rats were given a single gavage dose of 2.01 mg (14 $\mu\text{Ci}/\text{mg}$) or 6.4 mg (0.88 $\mu\text{Ci}/\text{mg}$) of ring- or ethyl-labeled cyanazine in peanut oil, respectively. The rats were kept in metabolism cages for 4 days, and their urine and feces were collected and assayed for radioactivity. Twelve female rats were given four gavage doses of ^{14}C -ring-labeled cyanazine in peanut oil over 8 days. Their feces were

collected and examined for radiolabeled metabolites. A single female rat was dosed with 1 mg of ring-labeled cyanazine. One hour after dosing, a biliary cannula was established. The bile and urine of this rat were collected for 20 hours.

Thin-layer chromatographs of the urine from rats given 2.0 mg (ring-labeled) and 6.4 mg (ethyl-labeled) cyanazine indicated the presence of seven and six metabolites, respectively. Five of the metabolites were identified. They included 2-chloro-4-amino-6-(1-cyano-1-methylethylamino)-S-triazine; N-acetyl-S-[4-amino-6-(1-cyano-1-methylethylamino)-S-triazinyl-2]-L-cysteine from the ring-labeled compound; and 2-chloro-4-(ethylamino)-6-(1-amino-1-methylamino)-S-triazine; N-acetyl-S-[4-(ethylamino)-6-(1-cyano-1-methylethylamino)-S-triazinyl-2]-L-cysteine; and 2-hydroxy-4-(ethylamino)-6-(1-carboxy-1-methylethylamino)-S-triazine from either labeled compound.

The fecal metabolites from rats given ring-labeled cyanazine accounted for ~50% of the radioactivity administered. Ten separate metabolites were isolated by paper chromatography. The major fecal metabolite (~25% of fecal radioactivity) was identified as 2-methoxy-4-(ethylamino)-6-(1-methylcarboxy-1-methylethylamino)-S-triazine. Other fecal metabolites were identified in minor amounts and included 2-hydroxy-4-amino-6-(1-carboxy-1-methylethylamino)-S-triazine; the S-P-bromobenzyl isothiuronium salt of 2-hydroxy-4-amino-6-(1-carboxy-1-methylethylamino)-S-triazine; 2-hydroxy-4-(ethylamino)-6-(1-amido-1-methylethylamino)-S-triazine; 2-hydroxy-4-ethylamino-6-(1-cyano-1-methylethylamino)-S-triazine; and 2-chloro-4-amino-6-(1-cyano-1-methylethylamino)-S-triazine. The major biliary metabolite (21% of administered radioactivity) from the bile duct cannulated rat given 1 mg of ring-labeled compound was S-[4-amino-6-(1-cyano-1-methylethylamino)-S-triazinyl-2]-glutathione. Two minor biliary metabolites were found, which

corresponded to the glutathione conjugate of the de-ethylated parent compound and its carboxylic acid. The authors postulated a mechanism for the metabolism of cyanazine in the rat:

1. Absorption and transport to the liver
2. N-desalkylation, glutathione conjugation or degradation to a carboxylic acid derivative
3. Biliary excretion of unconjugated and conjugated desethyl cyanazine, with subsequent reabsorption or fecal excretion.
4. Glutathione conjugates undergo gamma glutamyl-transferase action, peptidase action and N-acetylation to urinary mercapturic acids.
5. Partial reabsorption of 2-hydroxy carboxylic acid derivatives with urinary excretion.
6. Partial enterohepatic cycling of some metabolics.
7. Degradation of some glutathione conjugates to other simpler products.

4.4. EXCRETION

Orally-administered cyanazine is rapidly excreted by rats in their urine and feces (Hutson et al., 1970; Crayford and Hutson, 1972). About 33% of an oral dose of cyanazine was excreted in the urine of rats within 24 hours (Hutson et al., 1970). Biliary excretion of orally-administered (2,4,6-¹⁴C)-labeled cyanazine accounted for ~21% of the administered radioactivity 20 hours after administration. About 50% of the radioactivity contained in oral doses of (2,4,6-¹⁴C)-labeled cyanazine was found in the feces of rats within 4 days of administration (Hutson et al., 1970; Crayford and Hutson, 1972).

5. EFFECTS

5.1. CARCINOGENICITY

Cyanazine is not scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1983). Walker et al. (1974) found no increased incidence of tumors compared with controls in rats maintained on diets containing cyanazine in concentrations up to 100 ppm, or in dogs given cyanazine in capsules at doses up to 5 mg/kg/day for 2 years. This study is discussed more fully in Section 5.5.

5.2. MUTAGENICITY

The mutagenicity of cyanazine was equivocal in standard Ames-type assays using Salmonella typhimurium with or without mammalian activation (Eisenbeis et al., 1981; Moriya et al., 1983; Matijesevic et al., 1980a). Induction of mutation in certain strains of S. typhimurium has been observed when extracts of cyanazine-treated plant (maize) were added to the incubation and when maize homogenates were used for metabolic activation (Plewa, 1978; Matijesevic et al., 1980). Matijesevic et al. (1980b) observed an increase in mitotic gene conversion in yeast, especially when injected into a cyanazine-treated host mouse. When Drosophila melanogaster larvae were exposed to cyanazine, there may have been an increase in the number of dominant lethals, but this effect may have been caused by the toxicity to sperm (Murnik and Nash, 1977). Table 5-1 summarizes the available mutagenicity assays of cyanazine.

5.3. TERATOGENICITY

Lu et al. (1982) investigated the teratogenicity of technical Bladex in F344 rats. Mated rats were given gavage doses of 0, 1, 2.5, 10 or 25 mg Bladex/kg/day in aqueous 0.2% Methocel on days 6-15 of gestation. The vehicle and positive controls were Methocel and vitamin A (128 mg/kg/day on

TABLE 5-1
Mutagenicity Data for Cyanazine

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	plate incorporation	NR	± rat liver S-9	-	Also negative when tested in combination with atrazine, paraquat, sultan, cobex and sencor; Lasso; and Prowl and Paraquat.	Eisenbeis et al., 1981
Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	plate incorporation	≤5 mg/plate	± rat liver S-9	-	NC	Moriya et al., 1983
Reverse mutation	<i>S. typhimurium</i> TA98, TA1535	plate incorporation or liquid suspension	NR	none	+	NC	Mattijesevic et al., 1980a
Reverse mutation	<i>S. typhimurium</i> TA98, TA1535	plate incorporation or liquid suspension	10-60 ppm on maize	maize	+	The compound was applied to the growing plant followed by (time not indicated) preparation of an extract from the leaves. It was this extract which was tested.	Mattijesevic et al., 1980a
Reverse mutation	<i>S. typhimurium</i> TA98	plate incorporation	NR	none	-	Same as above	Plewa, 1978
Reverse mutation	<i>S. typhimurium</i> TA100	plate incorporation	NR	none	+	Same as above	Plewa, 1978
Reverse mutation	<i>S. typhimurium</i> TA100	plate incorporation	NR	plant (maize) activation	+	NC	Plewa, 1978
Reverse mutation	<i>Escherichia coli</i> WP2 hcr	plate incorporation	≤5 mg/plate	± rat liver S-9	-	NC	Moriya et al., 1983
Mitotic gene conversion	<i>Saccharomyces cerevisiae</i> D4	NR	NR	none	+	NC	Mattijesevic et al., 1980b
Mitotic gene conversion	<i>S. cerevisiae</i> D4	oral dose of Bladex, i.p. injection of <i>S. cerevisiae</i>	200-1000 ppm	Swiss mice	+	Increased conversion compared to <i>in vitro</i> assay.	Mattijesevic et al., 1980b
Dominant lethals	<i>Drosophila melanogaster</i>	larval injection or feeding	NR	NA	+	Apparent dominant lethal increase, but may have been due to sperm toxicity.	Murnik and Nash, 1977

NR = Not reported; NA = not applicable; NC = no comment

days 9-15 of gestation), respectively. Rats were killed and examined histopathologically on day 20 of gestation. Significantly reduced carcass weights compared to controls were observed in the 25 mg/kg/day group, but not in other treated groups. Reduced body weight gains were observed on gestation day 12 (at 10 and 25 mg/kg/day) and 15 (at 25 mg/kg/day). The incidence of the skeletal variation of lumbar spur in the 25 mg/kg/day group was observed to be significantly increased when compared to controls. No fetal toxicity was observed in other treatment groups. It was concluded that Bladex was not teratogenic at any dose tested because the fetal effects observed at 25 mg/kg/day were concomitant with maternal toxicity.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of cyanazine were not located in the available literature. (See Appendix for literature searched; also additional confidential information is available. See Chapter 8 for a more complete explanation.)

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Walker et al. (1974) studied the effects of subchronic and chronic oral administration of cyanazine in rats and dogs. In the subchronic study, cyanazine in the diet was administered to groups of 12 male and 12 female CFE rats at concentrations of 1.5, 3, 6, 12, 25, 50 and 100 ppm for 13 weeks. Groups of 36 rats/sex maintained on the basal diet served as controls. None of the rats died during the study or had any outward clinical or behavioral signs of toxicity. No specific data were reported; however, the investigators stated that at the 50 and 100 ppm levels there was reduced food consumption and body weight gain and changes in absolute organ weights and organ-to-body weight ratios (organs and direction of change not specified) that reflected the reduced growth rate. There were no effects on

hematologic parameters at any dietary level. Serum urea was increased in the 50 and 100 ppm groups and decreased in the 1.5 and 3 ppm groups. The changes in serum urea appeared to be unrelated to cyanazine treatment since the results of renal clearance studies performed on rats were unremarkable. At necropsy, no treatment-related effects were observed in viscera examined grossly or in a "wide range of tissues" that were examined microscopically. In a 2-year dietary study, cyanazine was administered at levels of 6, 12, 25 and 50 ppm to groups of 24 male and 24 female CFE rats (Walker et al., 1974). A group of 48 rats/sex served as controls. There were no outward clinical or behavioral signs of toxicity and no effects on mortality. No specific data were given, but the authors reported that the 50 ppm male and female groups and the 25 ppm female group had reduced body weight gain compared with controls. No statement regarding food consumption was made. There were no effects on organ weight, organ-to-body weight ratios, hematologic parameters or clinical chemistry values. There were no increased incidences of histopathological lesions (histology was performed on "a wide variety of tissues") or tumors in any treated group compared with controls.

In a 13-week study, cyanazine in gelatin capsules was administered orally to groups of four male and four female beagles at doses of 1.5, 5 and 15 mg/kg bw/day (Walker et al., 1974). Empty gelatin capsules were given to five male and five female control dogs. Dogs in the high-dose group vomited within 1 hour of dosing on the first 5 days of the study and had reduced body weight gain during the second half of the experiment. The high-dose female group had increased liver and kidney weights compared with controls; however, no specific data were reported. Results of hematologic and clinical chemistry tests and histological examination indicated no treatment-related effects.

Cyanazine in a gelatin capsule was administered orally to groups of four male and four female beagles at doses of 0.625, 1.25 and 5 mg/kg bw/day for 2 years (Walker et al., 1974). There were six male and six female control dogs. Male and female dogs of the high-dose group vomited within 1 hour of dosing on an average of once per week throughout the study. Growth rate was reduced throughout the study in the high-dose females and during the first 6 months in the high-dose males when compared with controls. High-dose females had reduced liver weights. Total serum protein was reduced in the high-dose groups. There were no other effects on hematologic parameters, clinical chemistry values or histopathology.

In the subchronic and chronic studies in rats and dogs, Walker et al. (1974) were not explicit about statistical significance. Such statistical tests as analysis of variance and Student's t-test were performed; therefore, the statistical significance of all reported changes was implicit in the study.

5.6. OTHER RELEVANT INFORMATION

The acute lethal toxicity of cyanazine has been studied in several species. Table 5-2 presents the available LD₅₀ values.

Cyanazine was not an irritant to the skin or eyes of rabbits, and was negative in skin sensitization studies in guinea pigs (Walker et al., 1974).

TABLE 5-2
Acute Lethal Toxicity of Cyanazine

Species	Route	LD ₅₀ (mg/kg)	Reference
Rat	oral	149	NIOSH, 1977
Rat	oral	334	WSSA, 1979
Rat	oral	182 (159-208)	Walker et al., 1974
Rat	dermal	>1200 (maximum dose tested)	Walker et al., 1974
Mouse	oral	380 (356-406)	Walker et al., 1974
Rabbit	oral	141 (88-254)	Walker et al., 1974

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

Available data on the toxicity of cyanazine to freshwater fish are limited to the LC_{50} s determined in four species common to United States waters (Johnson and Finley, 1980) and two Indian species (Rao and Dad, 1979). Three different formulations of cyanazine were tested in channel catfish and fathead minnows, all having similar lethal levels (Table 6-1). Rainbow trout was the most sensitive species tested by Johnson and Finley (1980), having a 96-hour LC_{50} of 9.0 mg/l when treated with 80% wettable cyanazine powder. The Indian species, Cirrhinus mrigala, had a 96-hour LC_{50} of 6.3 mg/l when exposed to an unspecified cyanazine compound. In fathead minnows and bluegills, lethality was not altered over a wide range of water hardness conditions. Dad and Tripathi (1980) reported that toxic effects of fish exposed to cyanazine included increased opercular beat, loss of color, increased mucous secretion and loss of equilibrium prior to death.

The 96-hour LC_{50} of technical cyanazine in the crustacean scud, Gammarus fasciatus, was 2.0 mg/l (Johnson and Finley, 1980). This fish-food species was, therefore, the most sensitive organism tested.

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic cyanazine exposure in aquatic species were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of cyanazine to aquatic plants or algae were not located in the available literature.

TABLE 6-1
Acute Lethal Effects of Cyanazine to Freshwater Fish

Species	Duration (hours)	LC ₅₀ (mg/l)	Method	Reference
Rainbow trout, <u>Salmo gairdneri</u>	96	9.0 ^a	static	Johnson and Finley, 1980
Bluegill sunfish, <u>Lepomis macrochirus</u>	96	22.5 ^a	static	Johnson and Finley, 1980
Channel catfish, <u>Ictalurus punctatus</u>	96	17.4 ^b	static	Johnson and Finley, 1980
	96	10.4 ^a	static	
	96	11.3 ^c	static	
Fathead minnow, <u>Pimephales promelas</u>	96	16.3 ^b	static	Johnson and Finley, 1980
	96	21.3 ^a	static	
	96	17.5 ^c	static	
<u>Sarotherodon massambicus</u>	96	11.3	NR	Rao and Dad, 1979
<u>Cirrhinus mrigala</u>	96	6.3	NR	

^a80% wettable powder

^bTechnical material ~100%

^cDispersible liquid 4 lb/gal

NR = Not reported

6.4. RESIDUE

In a study of the Des Moines River and Saylorville Reservoir, Leung (1980) indicated that cyanazine residues existed in water samples but fluctuated over a 1-year period. Residues were not detected in sediment samples or in seven species of fish. The author concluded that this herbicide did not accumulate.

6.5. OTHER RELEVANT INFORMATION

Additional data pertinent to the toxicity of cyanazine to aquatic organisms were not located in the available literature. (See Appendix for literature searched; also additional confidential information is available. See Chapter 8 for a more complete explanation.)

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The U.S. EPA has established tolerances for cyanazine residues of 0.05 ppm in or on cottonseed, corn and sorghum (Federal Register, 1971, 1975a,b) and 0.1 ppm in or on wheat grain and straw and wheat forage (Federal Register, 1978).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of cyanazine were not located in the available literature. (See Appendix for literature searched; also additional confidential information is available. See Chapter 8 for a more complete explanation.)

8. RISK ASSESSMENT

Sufficient data are not available to assess the carcinogenic potential of cyanazine. In the only study of long-term exposure to cyanazine, no increased incidences of tumors above control were observed in rats at dietary levels up to 100 ppm, or in dogs receiving cyanazine in capsules at doses up to 5 mg/kg/day for 2 years (Walker et al., 1974). When cyanazine was tested for mutagenicity in bacteria, positive results (Matijesevic et al., 1980a, Plewa, 1978) and negative results (Eisenbeis et al., 1981; Moriya et al., 1983) were reported. Positive results were obtained for mitotic gene conversion in yeast (Matijesevic et al., 1980b) and a questionably positive response was obtained for dominant lethal mutations in fruit flies (Murnik and Nash, 1977). Cyanazine administration to pregnant rats at 25 mg/kg/day on days 6-15 of gestation resulted in reduced body weight gain of dams and reduced carcass weight and increased incidence of lumbar spur in fetuses (Lu et al., 1982). No effects on dams or fetuses occurred at ≤ 10 mg/kg/day.

Because data are not sufficient to indicate that cyanazine is an animal carcinogen, it is appropriate to derive an ADI value for cyanazine based on toxicity. In a 2-year study in dogs, reduced body weight gain compared with controls occurred in male and female beagles treated at 5 mg cyanazine/kg/day (Walker et al., 1974). Female dogs at this dose level had reduced liver weights. No effects were observed at 1.25 mg/kg/day. Two-year dietary administration of cyanazine at 25 and 50 ppm to rats resulted in reduced body weight gain, with no other treatment-related effects on hematologic and clinical chemistry values or histopathology. There were no treatment-related effects in rats at 12 ppm cyanazine in the diet. Although no specific data were presented, Walker et al. (1974) considered 1.25 mg cyanazine/kg/day and

12 ppm cyanazine in the diet to represent NOELs for dogs and rats, respectively. Assuming that a rat consumes daily an amount of food equal to 5% of its body weight, $12 \text{ ppm} \times 0.05 = 0.6 \text{ mg/kg/day}$. Similarly, the 25 ppm level, which resulted in reduced body weight in rats, can be converted to an equivalent dose ($25 \text{ ppm} \times 0.05 = 1.25 \text{ mg/kg/day}$) that is equal to the NOEL for dogs. Therefore, it is appropriate to derive the ADI from the NOEL in rats. Applying an uncertainty factor of 100 for an animal NOEL in a chronic study, and assuming that a human weighs 70 kg, the ADI can be calculated to be 0.42 mg/human/day in the following manner:

$$\begin{aligned}\text{ADI} &= 0.6 \text{ mg/kg/day} \times 70 \text{ kg} \div 100 \\ &= 0.42 \text{ mg/day}\end{aligned}$$

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can be presented in this chapter.

The additional animal data reviewed in the CBI Appendix support the above NOELs and do not necessitate a change in the above ADI derivation.

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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